011683

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 27 1995



**MEMORANDUM**

SUBJECT: SECOND RfD/Peer Review Report of CADRE (AC 263,222)[(±)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methylnicotinic acid]

CASRN: 81334-60-3; ammonium salt: 104098-49-9
EPA Chem. Code: 129041; ammonium salt: 128943
Caswell No.: none; ammonium salt 946C

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on August 24, 1995 to discuss and evaluate the toxicology data submitted in support of AC 263,222 (CADRE) registration and associated permanent tolerances and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a multi-generation reproductive toxicity study in rats (83-4), and a battery of mutagenicity studies (84-2).

A. Background:

The Health Effects Division-RfD/Peer Review Committee met once before on April 21, 1994 to discuss and evaluate the toxicology data submitted in support of AC 263,222 (CADRE) registration for an experimental use permit and associated temporary tolerances and to assess a Reference Dose (RfD) for this chemical. Material available for review at that time consisted of data evaluation records (DERs) for a chronic (one-year) toxicity study in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), a subchronic toxicity study (3-month) in rats (82-1a) and a repeated-dose (21-day) dermal toxicity study in rats (82-2).

The Committee considered all the studies discussed in the previous meeting to be acceptable and the data evaluation records to be adequate.

The Committee was asked at the time of the last meeting to specifically address two issues: 1) whether a new chronic toxicity study in dogs would be required since the existing study failed to demonstrate a "no-observable effect level", and 2) whether maternal toxicity effects observed at the lowest dose level in the developmental toxicity study in rabbits and thought to be treatment-related were biologically significant and whether a new study would be required.

With respect to the first issue, the Committee determined that the overall "no-observable effect level" most likely would not be much lower than the "lowest-observable effect level" and, therefore, that a new study would not be required. With respect to the second issue, the Committee discounted the biological significance of what appeared to be maternal toxicity at the lowest dose level and recommended raising the "lowest-observable effect level". The study was considered to be acceptable.

A Reference Dose was also assessed for this chemical based on the data available at the time of the meeting (RfD report dated May 5, 1994).

B. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, MRID No. 43320307) to be acceptable as Core-Guideline data, and the data evaluation record for this study (HED Doc. No. 000000) to be adequate.

A chronic toxicity/carcinogenicity study in mice (MRID No. 43320306) submitted under 83-5 of Subdivision F of the Pesticide Assessment Guideline was available for review by the Committee. The Committee considered the chronic toxicity phase of the mouse study (83-1a, MRID No. 43320306) to be Core-supplementary data.

Regarding the one-year chronic toxicity study in dogs (83-1b, MRID No. 42711421), the Committee reaffirmed its prior conclusions that the effects observed at the lowest dose level were treatment-related, that the study is acceptable as Core-minimum data, and that a repeat study at lower dose levels is not necessary.

The Committee did not discuss the subchronic (3-month) toxicity study in rats (82-1a, MRID No. 42711419) because it was previously evaluated by the HED/RfD Committee on 4/21/1994.

The Committee agreed with the reviewer's evaluation and interpretation of the chronic toxicity data and recommended no

revisions to the data evaluation records as presented.

C. Carcinogenicity:

The Committee considered the carcinogenicity phases of the combined chronic toxicity/carcinogenicity studies in rats (83-2a, MRID No. 43320307) and mice (83-2b, MRID No. 43320306) to be acceptable. The highest dose levels tested in both the rat (20,000 ppm) and mouse (7,000 ppm) studies were considered to be a limit dose.

In rats, there were no treatment-related effects observed up to the highest dose level tested (20,000 ppm). Also, no treatment-related increase in tumors of any kind was observed at any dose level. Increased incidences of thyroid gland C-cell adenomas in males (15% in the high-dose males compared to 10% in controls), carcinomas (5% in the high-dose males compared to 0% in controls), and adenomas/carcinomas combined (20% in the high-dose males compared to 10% in controls) were observed. However, none of the increases was statistically significant ($p < 0.05$) by pair-wise comparison to the concurrent control group. Each of the increases also was within the historical control range for these types of tumors.

Historical control incidences for thyroid gland C-cell tumors in males submitted for three laboratories were: 1) Charles River 1984-1988; 0.0-17.4% (mean 6.4%) for C-cell adenomas and 0.0-6.7% (mean 2.3%) for C-cell carcinomas, 2) Pharmaco LSR; 1.3-18.8% (mean 8.9%) for C-cell adenomas and 0.0-5.7% (mean 1.1) for C-cell carcinomas, and 3) Hazleton Laboratories 1988-1992; 2.1-16.9% (mean 8.5%) for C-cell adenomas and 0.0-9.4% (mean 5.2%) for C-cell carcinomas.

Because the C-cell neoplasms observed in male rats were often microscopic, additional step-sectioning (4-sections/animal) of the thyroid glands of all male rats in the study was performed in order to identify additional neoplasms, if any. This technique resulted in revised incidences of adenomas of 17% in the high-dose males compared to 13% in controls, of carcinomas of 5% in the high-dose males compared to 0% in controls, and of adenomas/carcinomas combined of 22% in the high dose males compared to 13% in the controls. Statistical analysis of the step-sectioned data indicated no statistically significant ($p < 0.05$) positive trend or pair-wise differences between any treatment group and the control group.

In females, no increase in the incidences of C-cell adenomas and/or carcinomas of the thyroid gland was observed. In females, uterine stromal polyps and stromal polyps/stromal sarcoma combined appeared to be increased at the middle and high dose levels. The incidences of uterine stromal polyps were 1.6, 4.8, 7.7 and 7.7 % respectively, for the 0, 5000, 10000, and 20000 ppm groups. In the

high dose group, one stromal sarcoma also was observed. The incidences of the stromal polyps/stromal sarcoma combined were 1.6, 4.8, 7.7 and 9.2%, respectively, for the 0, 5000, 10000, and 20000 ppm groups. The increases in the stromal polyps/stromal sarcoma combined attained a statistically significant level for dose-response trend (P = 0.0383), but no statistically significant pair-wise difference (p = 0.0599) between the high dose group and the control groups was observed. The incidences were also within the historical control range for these types of tumors. Historical control incidences submitted for three laboratories were: 1) Charles River 1984-1988; endometrial stromal polyp 0.0-10.0% (mean 4.1%), endometrial stromal sarcoma 0.0-1.6% (mean 0.2%), 2) Pharmaco LSR; endometrial stromal polyp 0.0-8.8% (mean 3.4%), and 3) Hazleton Laboratories 1988-1992; endometrial stromal polyp 1.7-13.3% (mean 5.0%).

In mice, no treatment-related increase in tumors of any kind was observed at any dose level. The Committee, therefore, concluded that the treatment did not alter the spontaneous tumor profile in this strain of mouse.

On this basis, the Committee concluded that the chemical should be classified as **"Group E"**, evidence of non- carcinogenicity for humans; i.e. the chemical is **not likely** to be carcinogenic to humans via relevant routes of exposure. This weight of the evidence judgment is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies. It should be noted, however, that the designating of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

D. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 43320305) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. There were no treatment-related effects observed on parents or offspring. The NOEL was considered to be >1484 mg/kg/day in parental females and offspring. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study.

Two developmental toxicity studies in rats and rabbits were previously evaluated by the HED/RfD Committee on April 21, 1994, and therefore were not discussed by the Committee.

E. Acute and Subchronic Neurotoxicity:

No acute or subchronic neurotoxicity studies (81-8 and 82-7) were available for review by the Committee.

F. Mutagenicity:

The Committee considered the following mutagenicity studies to be acceptable:

1) Salmonella and E. coli WP2 uvrA-assay (MRID No. 42711424, HED Doc No. 010960): the test is negative up to 5000 µg/plate, the highest concentration tested.

2) Chinese hamster Ovary (CHO) cells/hgprt gene mutation assay (MRID No. 42711425, HED Doc. No. 010960): the test is negative up to 4000 µg/ml and 5000 µg/ml, the highest dose levels tested in the presence and absence of metabolic activation, respectively.

3) Chinese hamster Ovary (CHO) cells/chromosomal aberrations assay (MRID No. 42711427, HED Doc. No. 010960): the test is negative up to 2430 µg/ml, the highest concentration tested.

4) rat bone marrow/chromosomal aberrations assay (MRID No. 42711426, HED Doc. No.010960): the test is negative up to 5000 µg/kg, the highest dose level tested.

The Committee considered the following mutagenicity study to be unacceptable:

1) Unscheduled DNA synthesis (UDS)/primary rat hepatocytes (MRID No. 42711428, HED Doc. No.010960): the test is negative, but only insoluble concentrations were scored (up to 2500 µg/ml).

Overall, the Committee concluded that the four acceptable studies satisfy the initial testing battery of the current mutagenicity testing requirements and that, based on the available data, there is no concern for mutagenicity at this time.

G. Reference Dose (RfD):

The Committee recommended that an RfD for this chemical be established based upon the chronic toxicity study (1-year) in dogs with a lowest effect dose level (LOEL) of 5000 ppm (137 mg/kg/day for males, and 180 mg/kg/day for females). At this dose level, the lowest dose level tested, slight degeneration/necrosis and lymphocyte/macrophage infiltration in single skeletal muscle fibers were observed in both males and females and a slight decrease in creatinine levels was observed in females.

An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability and an additional UF of 3 was applied to account for the lack of an overall NOEL for the study. On this basis, the RfD was estimated to be 0.5 mg/kg/day.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and that an acceptable daily intake (ADI) has not been established by that Committee.

H. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Acting Chief, TB II), Stephen Dapson, Kerry Dearfield, Roger Gardner, Guruva Reddy, Esther Rinde, William Sette, Henry Spencer and Rick Whiting. In attendance also was Kit Farwell of HED as an observer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Ed Budd Edwin R. Budd

Karen Hamernik Karen R. Hamernik

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Marion Copley Marion Copley

CC: Stephanie Irene (HED/OPP)
Debra Edwards (HED/OPP)
Marion Copley (HED/OPP)
Kerry Dearfield (HED/OPP)
Karen Hamernik (HED/OPP)
Ed Budd (HED/OPP)
Albin Kocialski (HED/OPP)
Beth Doyle (HED/OPP)
AMAL Mahfouz (OW)
RfD File (SAB/HED)
Caswell File (HED/OPP)

I. Material Reviewed:

1. Fischer, J. E. (1994). AC 263,222: A chronic dietary oncogenicity and toxicity study in the albino rat. MRID No. 43320307, HED Doc. No. 000000. Classification: Guideline data. This study satisfies data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Fischer, J. E. (1994). A chronic dietary toxicity and oncogenicity study in the albino mouse with AC 263,222. MRID No. 43320306, HED Doc. No. 000000. Classification: Guideline data for carcinogenicity testing and Core-supplementary for chronic toxicity. This study satisfies data requirement 83-2b for carcinogenicity testing in mice and does not satisfy data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity in rodents.

3. Wolford, S. (1993). A one-year dietary toxicity study of AC 263,222 in dogs. MRID No. 42711421, HED Doc. No. 010960. Classification: Core-minimum data. This study was discussed by the Committee in the meetings of 4/21/1994 and 8/24/1995. It satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Schroeder, R. (1994). A two-generation (one-litter) reproduction study with AC 263,222 in rats. MRID No. 43320305, HED Doc. No. 000000. Classification: Guideline data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Schardein, J. L. (1992). Teratology study with AC 263,222 in rats. MRID No. 42711422, HED Doc. No. 010960. Classification: Core-minimum data. This study was discussed by the Committee in the meeting of 4/21/1994 and it satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. MacKenzie, K. M. (1992). A teratology study with AC 263,222 in rabbits. MRID No. 42711423, HED Doc. No. 010960. Classification: Core-minimum data. This study was discussed by the Committee in the meeting of 4/21/1994 and it satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

7. Fischer, J. E. (1992). AC 263,222: A 13-week dietary toxicity study in the albino rat. MRID No. 42711419, HED Doc. No. 010960. Classification: Guideline data according to the DER. This study was discussed by the Committee in the meeting of

4/21/1994 and it satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

8. Traul, K. A. (1992). Evaluation of AC 263,222 in a bacterial/ microsome mutagenicity assay. MRID No. 42711424, HED Doc. No. 010960. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for gene mutation testing.

9. Young, R. R. (1992). CHO/HGPRT forward mutation assay with AC 263,222. MRID No. 42711425, HED Doc. No. 010960. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for gene mutation testing.

10. Sharma, R. K. (1992). Evaluation of AC 263,222 in the in vitro chromosome aberration test in Chinese hamster ovary cells. MRID No. 42711427, HED Doc. No. 010960. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for structural chromosomal aberration testing.

11. Ivett, J. L. (1992). Chromosomal aberration in vivo in mammalian bone marrow cells with AC 263,222. MRID No. 42711426, HED Doc. No. 010960. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for structural chromosomal aberration testing.

12. Thilagar, A. (1992). Test for chemical induction of unscheduled DNA synthesis in rat primary hepatocyte cultures by autoradiography. MRID No. 42711428, HED Doc. No. 010996. Classification: Unacceptable. This study does not satisfy data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for testing for other genotoxic effects.